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(54) **Quaternary derivatives of noroxymorphone which relieve nausea and emesis.**

(57) Quaternary derivatives of noroxymorphone are used to prevent or relieve nausea and emesis associated with the use of narcotic analgesics without interfering with the analgesic activity of the drugs. A particularly preferred compound is methylnaltrexone. The compound is administered in a concentration between 0.05 mg/kg and 1.0 mg/kg prior to or concurrently with the administration of the narcotic analgesic.

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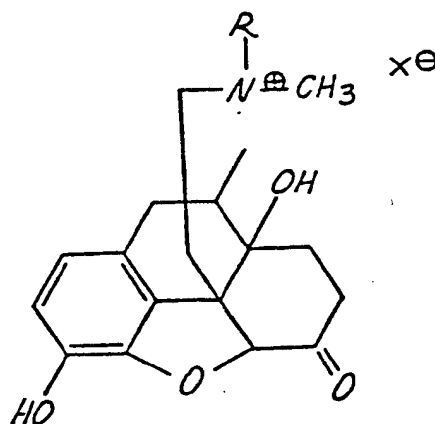
QUATERNARY DERIVATIVES OF NOROXYMORPHONE WHICH RELIEVE NAUSEA AND EMESIS

The administration of therapeutic doses of morphine and other clinically useful narcotic analgesics is often accompanied by unpleasant side effects on the gastro-intestinal system. For instance, morphine and related opiates such as meperidine and methadone may retard intestinal mobility by causing contractions of the small bowel circular smooth muscle.

Morphine and related narcotics may also induce nausea and increased mobility of the gastro-intestinal tract resulting in emesis or vomiting. These side effects are caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. (Goodman and Gilman, The Pharmacological Basis of Therapeutics, p. 502 [6th ed. 1980], incorporated herein by reference.) Studies have shown that morphine and other narcotics cause emesis in dogs. For example, Wang and Glaviano, JPET 111:329-334 (9143), incorporated herein by reference, reported that administration of 0.5 mg/kg of morphine intravenously to 12 dogs resulted in emesis in 9 dogs within an average of 2.4 minutes. (Mg/kg refers to milligrams of morphine per kilograms of body weight.) When 1.0 mg/kg of morphine was administered intramuscularly to 13 dogs, 12 of them vomited within an average time of 3.5 minutes.

U. S. Patent No. 4,176,186 of Goldberg et al disclosed treatment of intestinal immobility associated with the use of narcotic analgesics through the administration of quaternary derivatives of noroxymorphone. It has now been discovered that the same compounds are also useful for the treatment, both prophylactic and therapeutic, of the nausea and vomiting associated with the administration of these drugs.

According to the invention, therefore, nausea and vomiting by warm-blooded animals receiving morphine and related opiates, meperidine, methadone or the like, may be prevented or relieved by the administration of methylalaltrexone or other quaternary derivatives of noroxymorphone represented by the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

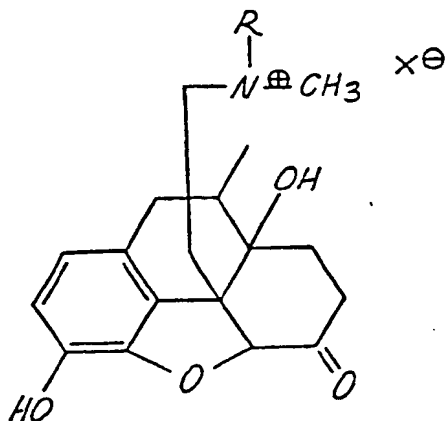
X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

These compounds are administered to the animal either prior to or simultaneously with the administration of the narcotic analgesic. They may be administered either enterally or parenterally. There has not been observed any interference with the analgesic activity of the opiates.

As used herein, unless the sense of the usage indicates otherwise, the term "morphine" refers to any narcotic analgesic.

DETAILED DESCRIPTION BY WAY OF EXAMPLE

This invention relates to the use of quaternary derivatives of noroxymorphone to prevent or relieve nausea and vomiting associated with the administration of morphine to warm-blooded animals. The useful compounds are represented by the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

The compounds are synthesized as described in United States Patent No. 4,176,186, the disclosure of which is incorporated herein by reference. A particularly preferred noroxymorphone derivative is methylnaltrexone, but other compounds represented by the above formula are also suitable.

Methylnaltrexone or other noroxymorphone derivatives may be administered to the patient either enterally or parenterally. However, a preferred method of administration is by injection. Nausea and emesis may follow after even a single dose of morphine, unlike intestinal immobility which is usually the effect of chronic repeated usage of the drug. Consequently, it is contemplated that the patient will be given an injection of methylnaltrexone prior to surgery or other occasion when morphine is used to treat acute pain.

As illustrated by the following Controls and Examples, our studies show that methylnaltrexone inhibits emesis when administered either together with the morphine or before the morphine is administered. It is thought that methylnaltrexone or other quaternary noroxymorphone derivatives may be administered up to two hours before the administration of morphine, but that period may be variable. In our studies, methylnaltrexone was administered intramuscularly by means of a syringe. Methylnaltrexone may also be administered enterally or parenterally by other means. It has been found to be effective in dosages in the range of about 0.05 mg/kg to about 1.0 mg/kg for each 1 mg/kg of administered morphine. It was found effective when administered in the same syringe as morphine and also when administered up to about one hour before the administration of morphine.

The effect of methylnaltrexone in reversing the emetic effects of morphine is illustrated herein. The

unit of mg/kg refers to milligrams of substance administered per kilograms of body weight.

CONTROL 1 AND EXAMPLE 1

One mg/kg of morphine was administered intramuscularly to five dogs. Four dogs vomited. In each instance, vomiting occurred within four minutes. On a different day the same dose of morphine was administered intramuscularly to the same five dogs in the same syringe with 1 mg/kg of methylnaltrexone. None of the dogs vomited.

CONTROL 2 AND EXAMPLE 2

Six dogs were given intramuscular doses of 1 mg/kg of morphine. All six dogs vomited. On an additional day the same dose of morphine was combined with 0.5 mg/kg of methylnaltrexone and administered in the same syringe to the same dogs. None of the dogs vomited.

CONTROL 3 AND EXAMPLE 3

One mg/kg of morphine was administered intramuscularly to three dogs. All three dogs vomited. On an additional day the morphine was combined with 0.25 mg/kg of methylnaltrexone and administered in the same syringe. None of the dogs vomited.

CONTROL 4 AND EXAMPLE 4

Methylnaltrexone was administered to two dogs prior to the administration of 1 mg/kg morphine. In one dog, 0.5 mg/kg of methylnaltrexone was administered intramuscularly 15 minutes before the morphine. No vomiting occurred. In the second dog, the same dose of methylnaltrexone was administered 30 minutes before the administration of morphine. No vomiting occurred.

CONTROL 5 AND EXAMPLE 5

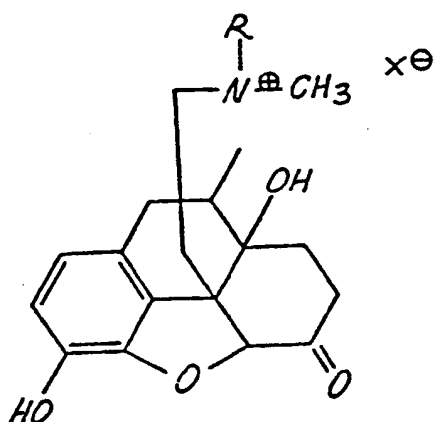
0.05 mg/kg methylnaltrexone was administered intravenously to four dogs one minute prior to the administration of 1.0 mg/kg morphine. No vomiting occurred in any of the dogs. On a different day, the same animals were given 1.0 mg/kg morphine without the administration of methylnaltrexone. All four dogs vomited.

The administration of methylnaltrexone alone was found to produce no noticeable effects in the

animals. Previous studies with larger doses of methylnaltrexone have demonstrated that unlike the non-quaternary naltrexone, methylnaltrexone does not precipitate withdrawal systems in morphine-tolerant dogs. Russell et al., *Eur. J. Pharmacol.* 78:255-261 (1982), incorporated herein by reference. Methylnaltrexone has not been found to interfere with the analgesic activity of morphine or narcotics.

Claims

1. Use of a compound of the formula:



wherein

R is allyl or a related radical e.g. chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, e.g. a chloride, bromide, iodide or methylsulfate anion for the manufacture of a medicament for preventing or relieving nausea and emesis associated with the use of narcotic analgesics in warm-blooded animals.

2. Use according to claim 1, where the compound is administered to the animal in an amount between 0.05 mg/kg and 1.0 mg/kg.

3. Use according to claim 1 or claim 2, where the compound is administered to the animal orally, or by injection.

4. Use according to claim 1 or claim 2, where the compound is administered to the animal parentally.

5. Use according to any one of claims 1 to 4 where the compound is administered to the animal prior to the administration of the narcotic analgesic.

6. Use according to claim 5 where the compound is administered to the animal up to about two hours prior to the administration of the narcotic analgesic.

7. Use according to any one of claims 1 to 4 where the compound is administered to the animal concurrently with the administration of the narcotic analgesic.

8. Use according to any one of claims 1 to 7 where the compound comprises methylnaltrexone.

9. Use of methylnaltrexone for the manufacture of a medicament for preventing or relieving nausea and emesis associated with the use of narcotic analgesics in warm-blooded animals by administering to an animal prone to exhibit nausea or emesis on administration of narcotic analgesics, the methylnaltrexone in the amount of between 0.05 mg/kg and 1.0 mg/kg simultaneous with or up to about two hours prior to the time of administration of the narcotic analgesic.

10. Use according to claim 9 where the methylnaltrexone is administered to the animal parentally.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 30 7999

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
D,Y	US-A-4 176 186 (L. I. GOLDBERG et al.) * claims *	1,9	A 61 K 31/485// C 07 D 489/08
Y	US-A-4 466 968 (J.E. BERNSTEN) * claim 1 *	1,9	
A	CHEMICAL ABSTSTRATS, vol. 100, no. 3, 16th January 1984, page 42, abstract no. 17503x; M. DRAGONETTI et al.: "Methyllevallorphan iodide (SR 58002), a potent narcotic antagonist with peripheral selectivity superior to that of other quaternary compounds"; & LIFE SCI. 1983, 33(Suppl. 1), 477-480	1	
A	CHEMICAL ABSTRACT, vol. 96, no. 21. 24th May 1982, page 60, abstract no. 174238f; J.C. KEITH, JR. et al.: "Failure of naloxone to prevent the emetic activity of apomorphine in dogs"; & J. VET. PHARMACOL. THER. 1981, 4(4), 315-316	1	
A	CHEMICAL ABSTRACTS, vol. 101, no. 25, 17th December 1984, page 19, abstract no. 222104e; M.A. IORIO et al.: "Narcotic agonist/antagonist properties of quaternary diastereoisomers derived from oxymorphone and naloxone", & EUR.J.MED.CHEM.-CHIM.THER. 1984, 19(4), 301-303	1	A 61 K 31/485 C 07 D 489/00
A	GB-A-1 202 148 (SANKYO CO. LTD.) * page 1, lines 35-60 *	1	
A	WO-A-8 303 197 (THE ROCKEFELLER UNIVERSITY)		
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 15-04-1988	Examiner HASS C V F
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

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